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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/523,285	02/03/2005	Christopher J. Dinsmore	21202YP	3814

210 7590 10/15/2007

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EXAMINER	
LOEWE, SUN JAE Y	
ART UNIT	**PAPER NUMBER**
1626	
MAIL DATE	**DELIVERY MODE**
10/15/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/523,285	DINSMORE ET AL.	
	Examiner	Art Unit	
	Sun Jae Y. Loewe	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *8-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 7* is/are rejected.

7)☒ Claim(s) *5 and 6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/9/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I in the reply filed on September 13, 2007 is acknowledged.

2. Claims 8-20 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected subject matter.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on June 9, 2005 was in compliance with the provisions of 37 CFR 1.97 and 37 CFR 1.98. The IDS was considered. A signed copy of form 1449 is enclosed herewith.

Claim Objections

4. Claim 1 objected to for containing non-elected subject matter.

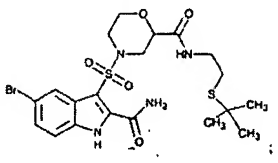
5. Claim 5 objected to because of the following informality: the Markush group is written in improper format. This objection may be overcome by inserting the word "and" between the following two entries:

5-Bromo-3-{[4-(3-phenylpropyl)piperidin-1-yl]sulfonyl}-1H-indole-2-carboxamide;

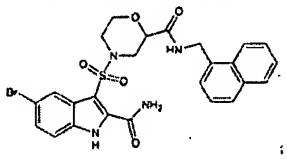
5-Bromo-N-methoxy-N-methyl-3-{[2-(phenoxymethyl)morpholin-4-yl]sulfonyl}-1H-indole-2-carboxamide;

6. Claim 6 objected to because of the following informality: the Markush group is written in improper format. This objection may be overcome by inserting the word "and" between the following two entries:

5-bromo-3-{[2-({[2-(tert-butylthio)ethyl]amino}carbonyl)morpholin-4-yl]sulfonyl}-1H-indole-2-carboxamide



5-bromo-3-{(2-{[(1-naphthylmethyl)amino]carbonyl}morpholin-4-yl)sulfonyl}-1H-indole-2-carboxamide



Claim Rejections - 35 USC § 112 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-4 and 7 under 35 USC 112 1st paragraph as failing to comply with the written description requirement.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41

USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

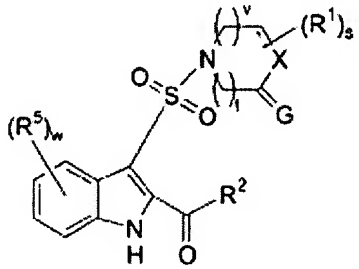
The MPEP states that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad genus. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The Guidelines for Examination of Patent Applications Under 35 USC 112, ¶1, "Written Description" Requirement (Federal Register, Vol. 66, No. 4, pg. 1105, column 3), in accordance with MPEP § 2163, specifically state that for each claim drawn to a genus the written description requirement may be satisfied through sufficient description of a representative number of species by a) actual reduction to practice; b) reduction to drawings or structural chemical formulas; c) disclosure of relevant, identifying characteristics (ie. structure) by functional characteristics coupled with a known or disclosed correlation between function and structure. The analysis of whether the specification complies with the written description requirement calls for the

examiner to compare the scope of the claim with the scope of the description to determine whether applicant has demonstrated possession of the claimed invention (Federal Register, Vol. 66, No. 4, p. 1105, 3rd column, 3rd paragraph). Below is such comparison.

I. Scope of Claims

Compounds of Formula II



II

The following variables are claimed *broader* than what is supported by the disclosure (see below section II).

R^2: for all claims
R^5: for all claims

II. Scope of Disclosure

Reduction to Practice:

The compounds reduced to practice support the following definitions for the variables:

R^2: $N(R^4)_2$ wherein R^4=hydrogen or unsubstituted alkyl
R^5: all variables with the following limitations

- R^a is hydrogen; unsubstituted alkyl
- R^6 is hydrogen; unsubstituted alkyl; alkyl substituted with phenyl/pyridinyl, phenyl or pyridinyl
- For R^5 = options 1-5, 7-10, 12-22
  - R^4 is hydrogen; unsubstituted alkyl; alkyl substituted with R^7=unsubstituted alkyl, halogen, CF_3
- For R^5 = options 6 and 11
  - R^4 is hydrogen; unsubstituted alkyl; alkyl substituted with R^7=unsubstituted alkyl, halo, CF_3, phenyl, pyridinyl, pyrazinyl, furanyl, benzofuranyl, thienyl, benzothienyl, thiazolyl, isoxazolyl, pyrrolyl; phenyl; pyridinyl; pyrazinyl;

furanyl; benzofuranyl; thienyl; benzothienyl; thiazolyl; isoxazolyl; pyrrolyl

Reduction to Structural or Chemical Formulas:

The only disclosure, in addition to the species reduced to practice, is in form of *lists* of possible groups (eg. benzimidazolyl, benzodioxolyl, benzofuranyl, benzofurazanyl, benzopyranyl, for heterocycle). This type of disclosure is not viewed to be a representation of any of the species it entails. A"laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species. MPEP 2163.I.A. and *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996). Therefore, there is no disclosure of species (eg. by reduction to structural/chemical formulas) in addition to those reduced to practice.

Correlation between Structure and Function:

A correlation between structure and function, for the instantly claimed genus of compounds, is neither known in the art nor disclosed in the specification. Thus, it is not understood what *specific structural elements* are *essential* for the activity of the instantly claimed compounds as inhibitors of tyrosine kinase.

III. *Analysis of Fulfillment of Written Description Requirement:*

The structure/activity relationship (SAR) for binding and activity is elucidated upon analysis of IC_{50} data (for example) of multiple compounds with various types of structural modifications. These types of studies provide insight into the structural limitations that are required for activity, ie. specific structural elements essential for the claimed activity. In the absence of such correlation, it is not possible to determine what structural modifications will allow for the preservation of the desired activity.

In conclusion: (i) substantial structural variation exists in the genus/subgenus embraced by claims 1-4 and 7; (ii) disclosure of species supporting genus is limited to compounds reduced to practice, which scope is not commensurate with the scope of genus/subgenus

claimed; (iii) common structural attributes of the claimed genus/subgenus, combined with a correlation between structure and function, is neither disclosed in the instant application nor commonly known in the art. Thus, the specification fails to provide adequate written description for the genus of compounds claimed and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

(Enablement)

8. Claims 1-4 and 7 rejected under 35 U.S.C. 112, first paragraph. The specification is *enabling* for the use of the compounds, and pharmaceutical compositions thereof, that have adequate written description. The specification is *not enabling* for the use of compounds, and pharmaceutical compositions thereof, that are not supported by the disclosure. In conclusion, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

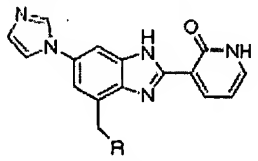
The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8USPQ2s 1400, 1404 (Fed. Cir. 1988). MPEP 2164.01(a) states "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue". The factors are applied below to the instant claims.

The breadth of the claims
Compounds not supported by the disclosure (see above section 7.I and 7.II.).

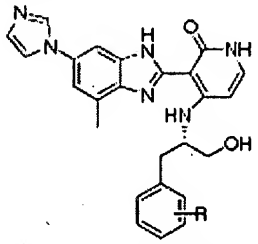
The nature of the invention
The compounds are disclosed to be inhibitors tyrosine kinase.

The state of the prior art/level of ordinary skill/level of predictability
The level of ordinary skill is high, but the level of predictability in the art is low. Although SAR studies are not available for the instantly claimed genus of compounds, these studies have been disclosed for different types of tyrosine kinase inhibitors. For example, see disclosure of Velaparthi et al. (excerpts below) which show that modest structural changes effect noticeable changes to the activity.

- Core Structure



  - For example, changing R from hydrogen to $-NH_2$ effected > 10-fold change in IGF-1R IC_{50} (μM).
- Core Structure



  - For example, changing R from hydrogen to 4-chloro effected 10-fold change in IGF-1R IC_{50} (μM).

As discussed in section 7, it is not known what structural limitations are required for preservation of activity within the genus claimed. In view of the level of predictability in the art for the claimed activity, one of ordinary skill would not know what structural modifications within the unrepresented genus (ie. unrepresented by the disclosure), if any, would lead to compounds that are active.

The amount of direction provided by the inventor/existence of working examples
No direction or working examples.

The quantity of experimentation needed to make or use the invention
It is not known which of the unrepresented compounds meet the structural requirements for activity. Thus, one of ordinary skill would not be enabled by the disclosure to make/use the claimed tyrosine kinase inhibitors. The amount of experimentation needed to practice the invention is undue.

Claim Rejections - 35 USC § 112

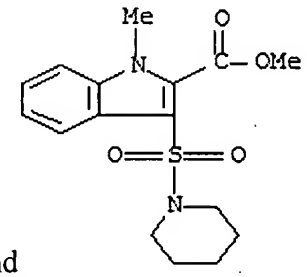
The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 2 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The definition of Formula II encompasses compounds wherein the carbon atom of the Markush alternative X has an incomplete valence (eg. X=C and $R^1_{s=0}$; eg. X=C and $R^1_{s\geq 1}$ wherein R^1 substitutes a carbon other than X). Appropriate correction and clarification is required.

Allowable Subject Matter

10. The compounds of Formula II appear to be allowable over the art of record. The closest prior art is the compound  taught by Szmuszkovicz wherein the indole nitrogen is substituted by a methyl. This compound does not have "utility" as its disclosure was solely for reporting a synthetic investigation. One of ordinary skill would not find the motivation/suggestion to change this structure to arrive at the instant invention (ie. unsubstituted indole nitrogen).

Conclusion

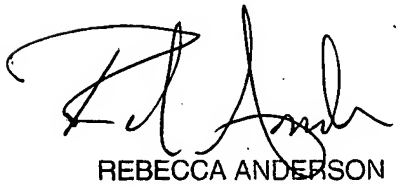
11. No claims allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sun Jae Y. Loewe whose telephone number is (571) 272-9074. The examiner can normally be reached on M-F 7:30-5:00 Est.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571)272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Sun Jae Y. Loewe
Art Unit 1626



REBECCA ANDERSON
PRIMARY EXAMINER